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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,435	03/20/2001	Kerstin Krieglstein	MBP-005XX	1324

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EXAMINER	
FORD, VANESSA L	
ART UNIT	PAPER NUMBER
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/19/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/786,435	KRIEGLSTEIN, KERSTIN	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/28/06*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,6,8 and 14-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,6,8 and 14-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

1. This action is responsive to Applicant's amendment and response filed June 28, 2006. Claims 2-4, 7 and 9-13 have been cancelled. Claims 1, 5, 6, 8 and 14-15 have been amended. Claims 1, 5-6, 8 and 14-18 are under examination. Applicant's submission of Exhibit I, (Massague, 1990), Exhibit II, (Table I, Massague, 1998) and Exhibit III, (Chang et I, 1997) are acknowledged.

2. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

Rejections Withdrawn

3. The following rejections are withdrawn:

a) rejection of claims 1 and 14-18 under 35 U.S.C. 102(b), pages 3-5 paragraph 4 of the previous Office Action.

b) rejection of claims 1 and 14-18 under 35 U.S.C. 103(a), pages 9-11 paragraph 6 of the previous Office Action.

c) rejection of claims 5-6 and 8 under 35 U.S.C. 103(a), pages 11-12 paragraph 7 of the previous Office Action.

Rejection Maintained

4. The rejection of under 35 U.S.C. 103(a) as unpatentable over Logan et al in view of Alexander et al and further in view of Mattson et al is maintained for claims 5-6 and 8 for the reasons set forth on pages 12-13, paragraph 11 of the previous Office

The rejection was on the grounds that Logan *(WO 93/19783)* teaches methods of for preventing, suppressing or treating a central nervous system pathology by contacting tissue with an agent (i.e. anti -TGF-β antibodies and TGF-β antagonists) that inhibits TGF-β activity (see the Abstract). Logan *(WO 93/19783)* teaches that after a penetrating injury of the brain or spinal cord (which include predamaged neurons), there is a failure of axonal growth (page 1). Logan *(WO 93/19783)* teaches that there are no therapies available to promote successful regeneration and functional reconnection of damaged neural pathways (predamaged neurons) (page 2). Logan *(WO 93/19783)* also teach that compositions containing the TGF-β inhibitors can be administered by infusion (i.e. intravenously) (Example 2). However, Logan teaches a method of administering agents including anti -TGF-β antibodies and TGF-β antagonists) to inhibit the activity of TGF-β in the central nervous system (page 3).

Logan *(WO 93/19783)* does not teach the use of compound for disintegrating blood clots.

Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage. Alexander et al teach that tissue plasminogen activator is effective in lysing blood clots in animals.

Mattson et al teach that neuroprotective factors such as TGF-β are expressed in response to brain injury (see the Abstract). Mattson et al teach that within minutes following traumatic brain injury, metabolic activity is rapidly depressed and edema and hemorrhage occurs (page 5).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the urokinse or tissue plasminogen activator of Alexandria et al to the pharmaceutical compositions comprising TGF-β antagonists of Logan *(WO 93/19783)* used in the method for inhibiting the biological activity of TGF on predamaged neurons in cerebral disorders because Mattson et al teach that within minutes following traumatic brain injury, metabolic activity is rapidly depressed and edema and hemorrhage occurs. Therefore, one of skill in the art would be motivated to add the urokinase and plasminogen activator as taught by Alexander et al because Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage. Additionally, Alexander et al has shown that tissue plasminogen activator is effective in lysing blood clots in animals. It would be expected barring evidence to the contrary that the addition of urokinase or

tissue plasminogen activator would disintegrate blood clots because it is well known in the art that the prevention of blood clots would be necessary for treatment of central nervous systems disorders to stop cerebral hemorrhaging.

Applicant's Arguments

A) Applicant urges that the present invention discloses the protection of predamaged or injured nerve cells by antagonizing the TGF-β mediated execution of neurons. Applicant urges that the claimed invention is important in neurodegenerative diseases such as ALS, Alzheimer's or Parkinson's disease. Applicant urges that in such neurodegenerative diseases scar formation is only a minor issue. Applicant urges that Logan et al describes the prevention of scar formation by antagonizing a second and obviously different effect of TGF-β proteins, namely the promotion of scarring by extracellular matrix material production. Applicant urges that Logan et al teach that TGF-β antagonists prevent scar formation but do not describe any impact of the TGF-β antagonists directly onto the injured nerve itself.

B) Applicant urges that there is no motivation to combine the prior art references to arrive at the claimed invention. Applicant urges that the other references do not overcome the deficiencies of Logan et al. Applicant urges that the rejection should be withdrawn.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed June 28, 2006 have been fully considered but they are not persuasive.

A) It should be remembered that this rejection is maintained for claims 5-8, which are drawn to a pharmaceutical composition comprising a first compound for preventing neuronal apoptosis by inhibiting the activity of TGF-β and a second compound for the disintegrating blood clots and a pharmaceutically acceptable carrier.

Logan et al teach pharmaceutical compositions comprising agents including anti - TGF-β antibodies and TGF-β antagonists) to inhibit the activity of TGF-β in the central nervous system. Logan teach that these inhibitors can be formulated with pharmaceutically acceptable carriers. Logan et al do not teach compounds for the disintegrating blood clots. However, Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage and disintegrating blood clots. One of skill in the art would be motivated to combine the two compounds into a pharmaceutical composition because Mattson et al teach that within minutes following traumatic brain injury, metabolic activity is rapidly depressed and edema and hemorrhage occurs. Mattson et al teach that TGF-β as well as other cytokines are released at the sign of injury. Therefore, one of skill in the art would be motivated to add the urokinase and/or plasminogen activator to a composition comprising TGF-β antagonists because Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral

hemorrhage. One skill in the art would reasonably conclude that a pharmaceutical composition comprising a TGF-β antagonist and a second compound for the disintegrating blood clots would be effective at treating and/or preventing further damage (e.g. blood clots and/or hemorrhage) caused by damage to the central nervous system. It should be remembered that the claims are drawn to a product and a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

B) To address Applicant's comments regarding establishing a case of *prima facie* obviousness, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

There is nothing on the record to suggest that the combination of prior art references do not teach the claimed invention.

New Grounds by of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1 and 15-18 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear as to who will benefit from the claimed method. What or who is being administered the compound? Clarification and/or correction is required.

6. Claims 1 and 15-18 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites "first compound". There is no second compound administered in the method steps of claim 1. Clarification and/or correction is required.

7. Claims 1 and 15-18 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The preamble of claim 1 recites "a method of preventing neuronal apoptosis..." followed by the step of providing a patient having damaged neurons...". It is unclear as to how neuronal apoptosis is prevented if the patient has damaged neurons. The language of claim 1 is unclear. Clarification and/or correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 14 and 18 are rejected under 35 U.S.C. 102(b) as anticipated by Henrich-Noack et al *(Stroke, 1996, Vol. 27, No.9, p. 1609-1615).*

Claims 1, 14 and 18 are drawn to a method for preventing neuronal apoptosis by inhibiting the biological activity of transforming growth factor TGF-β1, TGF-β2 and/or TGF-β-3 on damaged neurons in a cerebral disorder said method comprising providing a patient having damaged neurons in said patient with a first compound that prevents neuronal apoptosis by inhibiting the biological activity of TGF-β1, TGF-β-2 and/or TGF-β-3 on said damaged neurons.

Henrich-Noack et al teach that TGF-β1 protects hippocampal neurons against degeneration caused by transient global ischemia (see the Title and the Abstract). Henrich-Noack et al teach that rats with transient global ischemia were injected intracerebroventicularly with 4 ng TGF-β1, one hour before ischemia (see the Abstract). Henrich-Noack et al teach that administration of TGF-β1 reduced the percentage of damaged pyramidal cells and produced significant protection when injected directly into the hippocampal tissue (see the Abstract). Henrich-Noack et al anticipate the claimed invention.

9. Claims 1, 14 and 18 are rejected under 35 U.S.C. 102(b) as anticipated by Krieglstein et al *(European Journal of Pharmaceutical Sciences, 1997, Vol. 5, No.4, p. 181-187).*

Claims 1, 14 and 18 are drawn to a method for preventing neuronal apoptosis by inhibiting the biological activity of transforming growth factor TGF-β1, TGF-β2 and/or TGF-β-3 on damaged neurons in a cerebral disorder said method comprising providing a patient having damaged neurons in said patient with a first compound that prevents neuronal apoptosis by inhibiting the biological activity of TGF-β1, TGF-β-2 and/or TGF-β-3 on said damaged neurons.

Krieglstein et al disclose treatment of hippocampal neurons with TGF-β1 during the excitotoxic exposure and up to 18 hours thereafter, prevented neuronal injury concentration-dependently (pages 184-185, Figure 7).

Krieglstein et al disclose that TGF-β1 protects hippocampal neurons against degeneration caused by transient global ischemia (page 185, figure 8).
Krieglstein et al anticipate the claimed invention.

10. Claims 1 and 14-15 are rejected under 35 U.S.C. 102(b) as anticipated by Krieglstein et al *(Neurochemical Research, Vol.21, 1996).*

Claims 1 and 14-15 are drawn to a method for preventing neuronal apoptosis by inhibiting the biological activity of transforming growth factor TGF-β1, TGF-β2 and/or TGF-β-3 on damaged neurons in a cerebral disorder said method comprising providing a patient having damaged neurons in said patient with a first compound that prevents neuronal apoptosis by inhibiting the biological activity of TGF-β1, TGF-β-2 and/or TGF-β-3 on said damaged neurons.

Krieglstein et al teach that antibodies directed against TGF-β1, TGF-β-2 and TGF-β-3 reduced the biological activity of 3 ng/ml of TGF-β determined in an assay using mink lung epithelial cells (page 847, Figure 5).

Krieglstein et al anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1, 14 and 16-18 are rejected under 35 U.S.C. 103(a) as unpatentable over Henrich-Noack et al *(Stroke, 1996, Vol. 27, No.9, p. 1609-1615)* in view of

Alexander et al *(Neurosurgery, 1990, 26/4, p. 559-564)* and further in view of Mattson et al *(Journal of Neurotrama, Volume 11, Number 1, 1994).*

Claims 1, 14 and 16-18 are drawn to a method for preventing neuronal apoptosis by inhibiting the biological activity of transforming growth factor TGF-β1, TGF-β2 and/or TGF-β-3 on damaged neurons in a cerebral disorder said method comprising providing a patient having damaged neurons in said patient with a first compound that prevents neuronal apoptosis by inhibiting the biological activity of TGF-β1, TGF-β-2 and/or TGF-β-3 on said damaged neurons.

Henrich-Noack et al teach that TGF-β1 protects hippocampal neurons against degeneration caused by transient global ischemia (see the Title and the Abstract). Henrich-Noack et al teach that rats with transient global ischemia were injected intracerebroventicularly with 4 ng TGF-β1, one hour before ischemia (see the Abstract). Henrich-Noack et al teach that administration of TGF-β1 reduced the percentage of damaged pyramidal cells and produced significant protection when injected directly into the hippocampal tissue (see the Abstract).

Henrich-Noack et al teach do not teach the use of a second compound for disintegrating blood clots.

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following traumatic brain injury, metabolic activity is rapidly depressed and edema and hemorrhage occurs (page 5).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the urokinse or tissue plasminogen activator of Alexandria et al to the pharmaceutical compositions of Henrich-Noack et al comprising TGF-β-1 of used in the method for inhibiting the biological activity of TGF on damaged neurons in cerebral disorders because Mattson et al teach that within minutes following traumatic brain injury, metabolic activity is rapidly depressed and edema and hemorrhage occurs. Therefore, one of skill in the art would be motivated to add the urokinase and plasminogen activator as taught by Alexander et al because Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage. Additionally, Alexander et al has shown that tissue plasminogen activator is effective in lysing blood clots in animals. It would be expected barring evidence to the contrary that the addition of urokinase or tissue plasminogen activator would disintegrate blood clots because it is well known in the art that the prevention of blood clots would be necessary for treatment of central nervous systems disorders to stop cerebral hemorrhaging.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

13. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday –Thursday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Jeffery Siew can be reached at (571) 272-0787.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
December 10, 2006

NITA MINNIFIELD
PRIMARY EXAMINER